CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: **074832**

Trade Name : CAPTOPRIL AND HYDROCHLORTHIAZIDE TABLETS USP, 50MG/25MG

Generic Name: Captopril and Hydrochlorthiazide Tablets USP, 50mg/25mg

Sponsor : Danbury Pharmacal, Inc.

Approval Date: December 29 , 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074832

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074832

APPROVAL LETTERS

ANDA 74-832

DEC 29 1997

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

Dear Sir:

This is in reference to your abbreviated new drug application dated December 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Captopril and Hydrochlorothiazide Tablets USP, 50 mg/25 mg.

Reference is also made to your amendment dated December 3, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Captopril and Hydrochlorothiazide Tablets USP, 50 mg/25 mg, are bioequivalent and, therefore, therapeutically equivalent to the listed drug (Capozide® Tablets, 50 mg/25 mg, of E.R. Squibb and Sons, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

12/29/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074832

FINAL PRINTED LABELING

CAPTOPRIL and HYDROCHLOROTHIAZIDE Tablets, USP

Revised: September 1997A

USE IN PREGNANCY

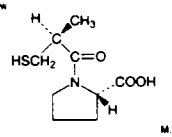
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, captopril and hydrochlorothiazide should be discontinued as soon as possible. **See WARNINGS: Captopril,** *Fetal/Neonatal Morbidity and Mortality*

DESCRIPTION

Captopril and hydrochlorothiazide tablets for oral administration combines two antihypertensive agents: captopril and hydrochlorothiazide. Captopril, the first of a new class of antihypertensive agents, is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Hydrochlorothiazide is a benzothiadiazide (thiazide) diuretic-antihypertensive.

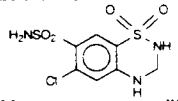
Captopril is designated chemically as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline; hydrochlorothiazide is 6-Chloro-3,4-dihydro-2*H*-1, 2, 4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/mL), methanol and ethanol and sparingly soluble in chloroform and ethyl acetate. The structural formula is represented below:



$C_9H_{15}NO_3S$ M.W. 217.29

Hydrochlorothiazide is a white crystalline powder slightly soluble in water but freely soluble in sodium hydroxide solution. The structural formula is represented below:



$C_7H_8ClN_3O_4S_2$ M.W. 297.75

Each tablet for oral administration contains 50 mg captopril and 25 mg hydrochlorothiazide. Each tablet also contains the following inactive ingredients: FD&C Blue No. 1, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and stearic acid.

CLINICAL PHARMACOLOGY

Captopril

Mechanism of Action

The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxyhydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies captopril did not alter the pressor responses to a number of other agents including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to "bradykininase" and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of captopril.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Pharmacokinetics

After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than two hours. In patients with renal impairment, however, retention of captopril occurs (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change or an increase in cardiac output. There is an increase in renal blood flow following administration of captopril and [illegible] is unchanged. In patients with

After oral administration of the above, about [illegible] absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average maximal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent as unchanged drug, most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than 3 hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than two hours. In patients with renal impairment, however, retention of captopril occurs (see **DOSAGE AND ADMINISTRATION**).

Pharmacodynamics

Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged. In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The maximum of effect is dose related and is extended in the presence of a thiazide-type diuretic. The full effect of a given dose may not be attained for 6 to 8 weeks (see **DOSAGE AND ADMINISTRATION**). The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect. Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

Hydrochlorothiazide

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.

Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.

The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.

The mean plasma half-life of hydrochlorothiazide in fasted individuals has been reported to be approximately 2.5 hours.

Onset of diuresis occurs in two hours and the peak effect at about four hours. Its action persists for approximately six to twelve hours. Hydrochlorothiazide is eliminated rapidly by the kidney.

INDICATIONS AND USAGE

Captopril and hydrochlorothiazide tablets are indicated for the treatment of hypertension. The blood pressure lowering effects of captopril and thiazides are approximately additive.

This fixed combination drug may be used as initial therapy or substituted for previously titrated doses of the individual components.

When captopril and hydrochlorothiazide are given together it may not be necessary to administer captopril in divided doses to attain blood pressure control at trough (before the next dose). Also, with such a combination, a daily dose of 15 mg of hydrochlorothiazide may be adequate.

Treatment may, therefore, be initiated with Captopril and Hydrochlorothiazide Tablets, USP 25 mg-15 mg once daily. Subsequent titration should be with additional doses of the components (captopril, hydrochlorothiazide) as single agents or as Captopril and Hydrochlorothiazide Tablets, USP 50 mg-15 mg, 25 mg-25 mg, or 50 mg-25 mg (see **DOSAGE AND ADMINISTRATION**).

In using captopril and hydrochlorothiazide, consideration should be given to the risk of neutropenia/agranulocytosis (see **WARNINGS**).

Captopril and hydrochlorothiazide may be used for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril and hydrochlorothiazide should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to other drug combinations.

ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see **WARNINGS: Angioedema**).

CONTRAINDICATIONS

Captopril

This product is contraindicated in patients who are hypersensitive to captopril or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

Hydrochlorothiazide

Hydrochlorothiazide is contraindicated in anuria. It is also contraindicated in patients who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS

Captopril

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including captopril and hydrochlorothiazide) may be subject to a variety of adverse reactions, some of them serious.

Angioedema

Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of treatment; some cases required medical therapy. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS: Captopril**.)

Anaphylactoid Reactions During Desensitization

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis

Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.5 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of

(See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS: Captopril**.)

Anaphylactoid Reactions During Desensitization:

Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure:

Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis

Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine $\geq$ 1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts, should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) the physician should withdraw captopril and closely follow the patient's course.

Proteinuria

Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 90 percent of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Hypotension

Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See **PRECAUTIONS: Drug Interactions**.)

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE-inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intrauterine environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

In general, lithium should not be given with diuretics (see **PRECAUTIONS: Drug Interactions**, *Hydrochlorothiazide*).

PRECAUTIONS

General

Captopril

Impaired Renal Function

Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion (see **CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings**).

Hyperkalemia

Elevations in serum potassium have been observed in some patients treated with ACE inhibitors including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See **PRECAUTIONS: Laboratory Tests and Drug Interactions**, *Captopril*; **ADVERSE REACTIONS: Altered Laboratory Findings**.)

Cough

Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia:

In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hemodialysis

Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors as medication. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. (See **WARNINGS: Captopril**: Anaphylactoid Reactions During Membrane Exposure.)

Hydrochlorothiazide

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance may include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, or when severe cirrhosis is present. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see **Drug Interactions**, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Latent diabetes mellitus may become manifest during thiazide administration.

The antihypertensive effect of thiazide diuretics may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen (BUN), a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Information for Patients

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See **WARNINGS: Captopril:** Angioedema.)

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

5

As patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. (See **PRECAUTIONS: General** and **Drug Interactions**, *Captopril*; **ADVERSE REACTIONS: Captopril**.)

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that captopril and hydrochlorothiazide tablets should be taken one hour before meals (see **DOSAGE AND ADMINISTRATION**).

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Laboratory Tests

Serum electrolyte levels should be regularly redetermined (see **WARNINGS: Captopril** and *Hydrochlorothiazide*; **PRECAUTIONS: General**, *Hydrochlorothiazide*).

Drug Interactions

Captopril

Hypotension — Patients on Diuretic Therapy

Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with captopril or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity

Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release

Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity

The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

Agents Increasing Serum Potassium

Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements, should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

Inhibitors of Endogenous Prostaglandin Synthesis

It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

Lithium

Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity (see **PRECAUTIONS: Drug Interactions**, *Hydrochlorothiazide*, Lithium).

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics—potentiation of orthostatic hypotension may occur.

Antidiabetics (oral agents and insulin)—since thiazides may elevate blood glucose levels, dosage adjustments of antidiabetic agents may be necessary.

Corticosteroids, ACTH—may intensify electrolyte imbalance, particularly hypokalemia. Monitor potassium levels; use potassium replacements if necessary.

Pressor amines (e.g., norepinephrine)—decreased arterial responsiveness, but not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Lithium—generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.

Nonsteroidal anti-inflammatory drugs—indomethacin or sulindac may reduce diuretic, natriuretic, and antihypertensive effects.

Cholestyramine and colestipol resins—Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH—intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine)—decreased arterial responsiveness.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)—possible increased responsiveness to the muscle relaxant.

Antidiabetics (oral agents and insulin)—dosage adjustments may be necessary since hydrochlorothiazide may affect glucose tolerance.

Drugs affecting renin-angiotensin system—effects of these agents may be potentiated; dosage adjustments may be required. Monitor and correct any fluid and electrolyte imbalances prior to surgery if feasible.

Nonsteroidal anti-inflammatory agents—in some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing or thiazide diuretics. Therefore, when hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Methenamine—possible decreased effectiveness due to alkalinization of the urine.

Pressor amines (e.g., norepinephrine)—decreased arterial responsiveness, but not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Use caution in patients taking both medications who undergo surgery. Administer preanesthetic and anesthetic agents in reduced dosage, and if possible, discontinue hydrochlorothiazide therapy one week prior to surgery.

Probenecid or sulfinpyrazone—increased dosage of these agents may be necessary since hydrochlorothiazide may have hyperuricemic effects.

Drug/Laboratory Test Interactions

Captopril

Captopril may cause a false-positive urine test for acetone.

Hydrochlorothiazide

MAO inhibitors—dosage adjustments of one or both agents may be necessary since hypotensive effects are enhanced.

Nonsteroidal muscle relaxants, anesthetics and anesthetics used in surgery (e.g., halogenated chloride and ether, cyclopropane)—effects of these agents may be potentiated; dosage adjustments may be required. Monitor and correct any fluid and electrolyte imbalances prior to surgery if feasible.

Nonsteroidal anti-inflammatory agents—in some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing or thiazide diuretics. Therefore, when hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Methenamine—possible decreased effectiveness due to alkalinization of the urine.

Pressor amines (e.g. norepinephrine)—decreased arterial responsiveness, but not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Use caution in patients taking both medications who undergo surgery. Administer prior to anesthetic and anesthetic agents in reduced dosage, and if possible, discontinue hydrochlorothiazide therapy one week prior to surgery.

Probenecid or sulfinpyrazone—increased dosage of these agents may be necessary since hydrochlorothiazide may have hyperuricemic effects.

Drug/Laboratory Test Interactions

Captopril

Captopril may cause a false-positive urine test for acetone.

Hydrochlorothiazide

Hydrochlorothiazide may cause diagnostic interference of the bentiromide test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Captopril

Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Studies in rats have revealed no impairment of fertility.

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP , however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of *Salmonella typhimurium* (Ames assay) and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in *in vivo* assay using *mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila* sex linked recessive lethal trait gene. Positive test results were obtained only in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Animal Toxicology

Captopril

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and vasculitis of arterial blood vessels.

Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.

Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 7 to 200 times the MRHD in rats and mice, at 20 to 60 times MRHD in monkeys, and at 30 times the MRHD in dogs.

Gastric erosions/ulcerations were increased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times MRHD in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD for only five to seven days.

In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-related fashion. The effect was first observed in the 86th week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Pregnancy: Categories C (first trimester) and D (second and third trimesters)

See WARNINGS: Captopril, *Fetal/Neonatal Morbidity and Mortality*

Pregnancy-Nonteratogenic Effects

Hydrochlorothiazide

Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers

Captopril and hydrochlorothiazide are excreted in human milk. Both captopril and hydrochlorothiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of captopril and hydrochlorothiazide tablets to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population: dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and subsequent complications, including oliguria and seizures, have been reported.

Captopril and hydrochlorothiazide tablets should be used in pediatric patients only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS

Captopril

Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About one of 100 patients developed proteinuria (see WARNINGS).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS: Drug Interactions.

Renal: About one of 100 patients ...

WARNINGS:

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic: Neutropenia/agranulocytosis has occurred (see **WARNINGS**). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see **WARNINGS** and **PRECAUTIONS: Drug Interactions** for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See **WARNINGS: Captopril:** Angioedema and **PRECAUTIONS:** Information for Patients.)

Cough: Cough has been reported in 0.5 - 2% of patients treated with captopril in clinical trials (see **PRECAUTIONS: General,** *Captopril,* Cough).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, epithelial ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesia.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a Whole: Anaphylactoid reactions (see **WARNINGS: Captopril:** *Anaphylactoid and Possibly Related Reactions* and **PRECAUTIONS:** *Hemodialysis*).

General: asthenia, gynecomastia.

Cardiovascular: cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.

Dermatologic: bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal: pancreatitis, glossitis, dyspepsia.

Hematologic: anemia, including aplastic and hemolytic.

Hepatobiliary: jaundice, hepatitis, including rare cases of necrosis, cholestasis.

Metabolic: symptomatic hyponatremia.

Musculoskeletal: myalgia, myasthenia.

Nervous/Psychiatric: ataxia, confusion, depression, nervousness, somnolence.

Respiratory: bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses: blurred vision.

Urogenital: impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality

See **WARNINGS: Captopril,** *Fetal/Neonatal Morbidity and Mortality.*

Hydrochlorothiazide

Gastrointestinal System: anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis.

Central Nervous System: dizziness, vertigo, paresthesias, headache, and xanthopsia.

Hematologic: leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia.

Cardiovascular: orthostatic hypotension.

Hypersensitivity: purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions.

Other: hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Potential Clinical Laboratory Findings

Serum Electrolytes: Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see **PRECAUTIONS:** *Captopril*).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE

Captopril

Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril. There is no information concerning exchange transfusion for removing captopril from the general circulation.

Hydrochlorothiazide

In addition to the expected diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with abnormal depression of respiration and cardiovascular functions and without evidence of serum electrolyte changes or dehydration. The mechanisms of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. The degree to which hydrochlorothiazide is removed by hemodialysis has not been clearly established. Measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal functions should be instituted.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED ACCORDING TO THE PATIENT'S RESPONSE.

Captopril and hydrochlorothiazide tablets may be substituted for the previously titrated individual components.

Alternatively, therapy may be instituted with a single tablet of captopril and hydrochlorothiazide 25 mg-15 mg taken once daily. For patients insufficiently responsive to the initial dose, additional captopril or hydrochlorothiazide may be added as individual components or by using Captopril and Hydrochlorothiazide Tablets 50 mg-15 mg, 25 mg-25 mg or 50 mg-25 mg, or divided doses may be used.

Because the full effect of a given dose may not be attained for 6 to 8 weeks, dosage adjustments should generally be made at 6 week intervals, unless the clinical situation demands more rapid adjustment.

In general, daily dosage of captopril should not exceed 150 mg and of hydrochlorothiazide should not exceed 50 mg.

Captopril and hydrochlorothiazide tablets should be taken one

hemodialysis there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

Hydrochlorothiazide

In addition to the expected diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. The degree to which hydrochlorothiazide is removed by hemodialysis has not been clearly established. Measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function should be instituted.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED ACCORDING TO THE PATIENT'S RESPONSE.

Captopril and hydrochlorothiazide tablets may be substituted for the previously titrated individual components.

Alternatively, therapy may be instituted with a single tablet of captopril and hydrochlorothiazide 25 mg-15 mg taken once daily. For patients insufficiently responsive to the initial dose, additional captopril or hydrochlorothiazide may be added as individual components or by using Captopril and Hydrochlorothiazide Tablets 50 mg-15 mg, 25 mg-25 mg or 50 mg-25 mg, or divided doses may be used.

Because the full effect of a given dose may not be observed for 4 to 8 weeks, dosage adjustments should generally be made at 4 week intervals, unless the clinical situation demands more rapid adjustment.

In general, daily doses of captopril should not exceed 150 mg and of hydrochlorothiazide should not exceed 50 mg.

Captopril and hydrochlorothiazide tablets should be taken one hour before meals.

Dosage Adjustment in Renal Impairment—Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses of captopril and hydrochlorothiazide.

After the desired therapeutic effect has been achieved, the dose intervals should be increased or the total daily dose reduced until the minimal effective dose is achieved. When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic is preferred for use with captopril; therefore, for patients with severe renal dysfunction the captopril and hydrochlorothiazide combination tablet is not usually recommended. (See **WARNINGS: Captopril:** Anaphylactoid Reactions During Membrane Exposure and **PRECAUTIONS:** *Hemodialysis.*)

HOW SUPPLIED

Captopril and Hydrochlorothiazide Tablets, USP 50 mg-25 mg are scored, oval-shaped, blue tablets imprinted "58 12" and "DAN" supplied in bottles of 100, 500 and 1000.

Dispense in a light container with a child-resistant closure.

Do not store above 86°F. Keep bottles tightly closed.

Protect from moisture.

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

Revised: September 1997A

8

SCHEIN
PHARMACEUTICAL

NDC 0364-2640-01 100 Tablets

CAPTOPRIL and HYDROCHLOROTHIAZIDE
Tablets, USP

50 mg-25 mg

Caution: Federal law prohibits dispensing without prescription.

Each tablet contains:
Captopril, USP, 50 mg
Hydrochlorothiazide, USP, 25 mg

Dosage: See package insert for dosage and full prescribing information.

Dispense in a tight container with a child-resistant closure.

DO NOT STORE ABOVE 86°F. Keep bottles tightly closed.

Protect from moisture.

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2640-01 5

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2640-05 500 Tablets

CAPTOPRIL and HYDROCHLOROTHIAZIDE
Tablets, USP

50 mg-25 mg

Caution: Federal law prohibits dispensing without prescription.

Each tablet contains:
Captopril, USP, 50 mg
Hydrochlorothiazide, USP, 25 mg

Dosage: See package insert for dosage and full prescribing information.

Dispense in a tight container with a child-resistant closure.

DO NOT STORE ABOVE 86°F. Keep bottles tightly closed.

Protect from moisture.

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2640-05 5

Control Number and Expiration Date

SCHEIN
PHARMACEUTICAL

NDC 0364-2640-02 1000 Tablets

CAPTOPRIL and HYDROCHLOROTHIAZIDE
Tablets, USP

50 mg-25 mg

Caution: Federal law prohibits dispensing without prescription.

Each tablet contains:
Captopril, USP, 50 mg
Hydrochlorothiazide, USP, 25 mg

Dosage: See package insert for dosage and full prescribing information.

Dispense in a tight container with a child-resistant closure.

DO NOT STORE ABOVE 86°F. Keep bottles tightly closed.

Protect from moisture.

Mfd. by: Danbury Pharmacal, Inc.
Subsidiary of
Schein Pharmaceutical, Inc.
Florham Park, NJ 07932 USA

A-A

N 3 0364-2640-02 4

Control Number and Expiration Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074832

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 74-832

3. NAME AND ADDRESS OF APPLICANT
Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

4. BASIS OF SUBMISSION Capozide® of Squibb; Paragraph III cert. Pat. #4,217,347 expiring on December 27, 1997.

5. SUPPLEMENT(s) N/A 6. PROPRIETARY NAME none

7. NONPROPRIETARY NAME Captopril and Hydrochlorothiazide USP.

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

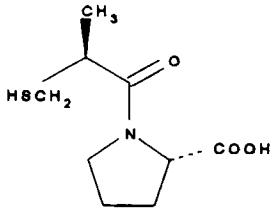
9. AMENDMENTS AND OTHER DATES:
December 29, 1995 Date of application.
December 3, 1997 Amendment

10. PHARMACOLOGICAL CATEGORY ACE inhibitor and diuretic.

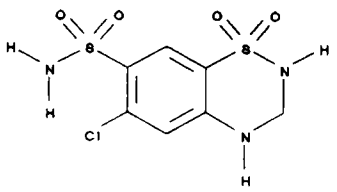
11. Rx or OTC Rx 12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM 500 14. POTENCY 50mg/25mg

15. CHEMICAL NAME AND STRUCTURE
Captopril USP $C_9H_{15}NO_3S$; M.W. = 217.28
1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline. CAS [62571-86-2]



Hydrochlorothiazide USP $C_7H_8ClN_3O_4S_2$;
M.W. = 297.73; 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide. CAS [58-93-5]



16. RECORDS AND REPORTS N/A

17. COMMENTS: Firm submitted a minor amendment dated 12/3/97 stating that there are no changes in the conditions under which the product was tentatively approved on 10/10/97 including labeling and CMC.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER: Jim Fan DATE COMPLETED: 12/11/97

cc: ANDA 74-832
DUP File
Division File
Field Copy
Endorsements:

HFD-623/J.Fan' 12/11/97 2/12/98
HFD-623/V.Sayeed, Ph.D.
x:\new\firmsam\danbury\ltrs&rev\74832na3.cr
F/T by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074832

BIOEQUIVALENCE REVIEW(S)

ANDA 74-832

NOV 25 1996

Danbury Pharmacal, Inc.
Attention: James O. Kelly
131 West Street
Danbury, CT 06810

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Captopril and Hydrochlorothiazide Tablets, 25 mg and 50 mg, and to our letter dated June 10, 1996.

Reference is also made to your amendments dated August 16, October 2 and November 5, 1996.

Our June 6 letter notified Danbury that for the hydrochlorothiazide component of the product, an interim dissolution specification of of the labeled amount of the ingredient in minutes was acceptable. It has subsequently been determined that this dissolution specification was not sufficiently discriminatory to confirm the quality of the product. Following discussions with you and the above referenced amendments, the following revised dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 Apparatus I (basket) at 50 rpm. The test product should meet the following specifications:
>
> > Not less than of the labeled amount of captopril in the dosage form is dissolved in 20 minutes and not less than of the labeled amount of hydrochlorothiazide in the dosage form is dissolved in **30** minutes.

These dissolution specifications should be regarded as interim specifications until FDA and USP finalize new dissolution specifications for Captopril and Hydrochlorothiazide Tablets.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Captopril and Hydrochlorothiazide Tablets

50 mg/25 mg Tablets

ANDA #74-832

Reviewer: Moo Park

Filename: 74832A.896

Danbury Pharmacal

Danbury, CT

Submission Date:
December 29, 1995
August 16, 1996
October 2, 1996
November 5, 1996

Review of Three Amendments

I. Objectives

To review Danbury's two amendments submitted via FAX regarding its dissolution specifications for hydrochlorothiazide. It was found that the contents of the three amendments are exactly same. The amendment contains dissolution data for lot #11919C up to 24 months in four different packages. The same data were sent to USP as of September 18, 1996 for reconsideration of USP proposal.

II. Background

Danbury's *in vivo* bioequivalence study demonstrated that Danbury's Captopril and Hydrochlorothiazide Tablets, 50 mg/25 mg, is bioequivalent to Bristol-Myers Squibb's Capozide® Tablets, 50 mg/25 mg. However, Danbury's dissolution data for hydrochlorothiazide component in the Captopril and Hydrochlorothiazide Tablets, 50 mg/25 mg strength, concerned the Division of Bioequivalence since Danbury proposed its own specifications and there are at least three additional sets of specifications as summarized below:

Danbury's proposed specifications:
Medium: 0.1N Hcl; 900 mL
Apparatus: Basket(I); 50 rpm
Tolerances: captopril: NLT in 20 min
HCT: NLT in 60 min

Current FDA's specifications: This will be discarded in favor of the current NDA specifications.
Medium: 0.1N Hcl; 900 mL
Apparatus: Basket(I); 100 rpm
Tolerances: captopril: NLT in 30 min

HCT: NLT .n 60 min

Current NDA specifications:
Medium: 0.1N Hcl; 900 mL
Apparatus: Basket(I); 50 rpm
Tolerances: captopril: NLT in 20 min
HCT: NLT in 30 min

Pharmacopeial Forum specifications (revised):
Medium: 0.1N Hcl; 900 mL
Apparatus: Basket(I); 50 rpm
Tolerances: captopril: NLT in 20 min
HCT: NLT in 30 min

The Division of Bioequivalence suggested Danbury to tighten its dissolution specifications for hydrochlorothiazide. Danbury responded to the Division with the amendment.

III. Comments

1. The stability data submitted by Danbury for lot #11919C up to 24 months in four different packages show similar pattern among the different package sizes. The following summary was obtained by analyzing the 100 tablets package size:

   Dissolution data obtained at: 30 min
   Total number of testing in 24 months: 11 testings
   Number of means which are 5
   Minimum mean dissolution: with 10.1% CV
   Maximum mean dissolution: with 7.7% CV
   Average of the means: with 7.2% mean CV

2. Danbury commented that their dissolution data for hydrochlorothiazide meet the NDA specifications of **NLT in 30 min**, not the revised pharmacopeial forum specifications of **NLT in 30 min.**

3. Moo Park developed a method of estimating Q value for dissolution specifications. The method involves the use of mean dissolution from 6-12 units (12 units are preferable.) with their %CV. Lower confidence limits of 95% or 99% confidence intervals (99% confidence intervals are preferable.) are plotted against mean dissolution with a particular %CV. The Q value is the lower 99% confidence limit where the mean dissolution meets with the confidence line constructed under a particular %CV. Figures 1-3 represents the confidence lines prepared at three different %CV levels, 5%, 10% and 15%.

   Danbury's data in the comment #1 indicates that Fig 2 with %CV of 10 can be used to estimate the appropriate Q value.

With the dissolution mean of , we obtain the lower 99% confidence limit of The Q values are conventionally a multiple of 5. Therefore, it appears that Q value for Danbury's hydrochlorothiazide should be in 30 min.

4. The Division of Bioequivalence agrees with Danbury's estimation of specifications for hydrochlorothiazide.

5. Danbury's dissolution data for hydrochlorothiazide are variable. The firm did not provide convincing explanation for possible cause of the variability.

6. Danbury accepts the NDA specifications and discards the original proposal of in 60 min for hydrochlorothiazide..

IV. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Danbury on its Captopril and Hydrochlorothiazide Tablets, 50 mg/25 mg, lot #11919C, comparing it to Bristol-Myers Squibb's Capozide[R] Tablets, 50 mg/25 mg, Lot #2L51505, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Danbury's Captopril and Hydrochlorothiazide Tablets, 50 mg/25 mg, is bioequivalent to Bristol-Myers Squibb's Capozide[R] Tablets, 50 mg/25 mg.

2. The USP dissolution testing conducted by Danbury on its Captopril and Hydrochlorothiazide Tablets, 50 mg/25 mg, lot #11919C, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 Apparatus I (basket) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of captopril in the dosage form is dissolved in 20 minutes and not less than of the labeled amount of hydrochlorothiazide* in the dosage form is dissolved in 30 minutes.

*Dissolution specifications for hydrochlorothiazide are interim.

4. From the bioequivalence point of view the firm has met the *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

The firm should be informed of the recommendations.

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE _____ 11/15/96

Concur: _____ Date: 11/18/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA # 74-832 (original, duplicate), Park, Drug File, Division File

File history: Draft (10/11/96); Final (11/15/96)